

PAM plus probenecid and procaine penicillin plus probenecid in gonorrhoea

A. L. HILTON

The Royal Infirmary, Doncaster

In 1944, when gonorrhoea responded to 100,000 units of crystalline penicillin given in divided doses, Miller, Scott, and Moeller (1944) observed that the gonococcus was cleared from the urethral secretions within 1 to 6 hours. 23 years later, Holmes, Johnson, and Floyd (1967), in the Far East, noted that only one case, a therapeutic failure, out of twenty treated with 2.4 m.u. procaine penicillin with probenecid, continued to yield gonococci from the urethra after 9 hours. Supporting this evidence of rapid bacterial eradication are the results of treatment with sodium penicillin and probenecid, producing a very high but relatively short-lived penicillinaemia (Jensen, Kvorning, and Norredam, 1963; Olsen and Lomholt, 1969). The straightforward 'one-shot' treatment has still much to commend it; it deals with the problem of those who default from a second injection and prevents the hoarder of tablets from masking his next infection. In keeping with this tradition, Cobbold, Morrison, Spitzer, and Willcox (1970) prescribed 1.2 m.u. procaine penicillin alone or with 1 g. probenecid; the addition of the latter reduced the recurrence rate from 13 to 7.2 per cent.

The renal-blocking agent probenecid has had a good record (Boger and Strickland, 1955). Some nausea and vomiting may occur, anaphylaxis is a rare complication, and uric acid crystalluria with deleterious effects on the kidney is a very remote possibility.

When the emergence of relatively resistant gonococci first presented a significant problem, Curtis and Wilkinson (1958) suggested that a preparation of penicillin should be devised to yield a blood concentration of not less than 1 unit penicillin per ml. persisting for 24 hours. This principle implies a high initial concentration of penicillin, probably the most important requirement to attack the more resistant organisms (Krook and Juhlin, 1965), and a rapid 'tailing off'. To match this proposition, Hilton (1959) used 1.2 m.u. procaine penicillin in arachis oil with

2 per cent. aluminium monostearate (PAM) together with probenecid 0.5 g. initially and thereafter 6-hrly for three doses. In 1966, all the available sources of PAM dried up and procaine penicillin 1.2 m.u. was substituted. This paper presents the results of treatment of 405 cases of gonorrhoea from 1964 to July 1969, with probenecid and PAM (or, later, procaine penicillin) in the dosage described; the results are related to the sensitivity to penicillin of the strains of the gonococci isolated in culture in the majority of cases by work carried out at the Wakefield Public Health Laboratory under the direction of Dr. L. A. Little.

Materials and methods

All male patients attending the Doncaster Royal Infirmary with gonococcal urethritis confirmed by culture and treated with penicillin have been included; cases are also mentioned in which culture was not successful and diagnosis was based on smears confirmed by positive results in a duplicate smear examined in the laboratory.

Diagnosis and treatment

The diagnosis was made on the findings in Gram-stained smears of the urethral discharge, and treatment as described was given in all cases but three in which ethebenecid was substituted for probenecid. A second urethral smear was prepared and this, together with the urethral swab in Stuart's transport medium, was posted to Wakefield. Positive cultures were reported by telephone 3 to 4 days later during the next clinic session. Specimens from cases of treatment failure were also cultured and, if nongonococcal urethritis developed, treatment was delayed as long as possible to avoid mistaking it for a relapse of gonorrhoea. Results of sensitivity tests were available during the week after the first attendance.

Relapse or re-infection

It was decided to accept all recurrences of gonorrhoea within 2 weeks of the initial treatment as relapses. In fact, only one patient with a recurrence of gonorrhoea, as defined, after treatment admitted further exposure to risk with the possibility of re-infection.

Sensitivity testing

The Wakefield Public Health Laboratory serves many clinics in the populous West Riding of Yorkshire. The Director, Dr. L. A. Little, had found during the Medical Research Council Study (M.R.C., 1961) that most strains of gonococci fell into two groups: one sensitive to 0.06 units penicillin per ml. or less, and the other sensitive to between 0.06 and 0.5 units/ml. He decided in 1965 to test gonococcal sensitivity on solid media using one control plate, one incorporating penicillin at a dilution of 0.05 units/ml., and one with 0.5 units/ml. If growth was inhibited on the second plate, the strain was classified as fully sensitive, and if on the third as partially resistant to penicillin. The 1964 sensitivity levels have been adjusted to lie between these two readings.

Results

RECURRENCE RATE

In the first group of 160 cases, seen in 1964 to 1966, among 143 followed there was a relapse rate of 2.1 per cent. In the second group of 216 cases seen in 1966 to 1969, among 191 followed the relapse rate was 6.8 per cent. (Table I). There were fifty additional cases in which culture was not successful; eleven in the first and 39 in the second period. If these are taken into account the final relapse rates were 1.8 and 5.1 per cent. respectively. Nongonococcal urethritis arose mainly in the second and third months in both groups.

SENSITIVITY LEVELS

Table II shows the relapse rate by years. Out of the total of 376 cases sensitivity tests were successful in 355; 21 strains were lost on subculture. The partially resistant organisms formed 18.1 and 31.7 per cent. of the two groups respectively. In the period 1967 to 1969, there were 26 strains from cases given treatment other than penicillin; if these are included, the proportion of partially resistant organisms amounted to 31.1 per cent. of 237 strains. Included in these 26 was a case treated with Kanamycin in 1967 in which the organism was resistant to 0.5 units penicillin per ml. This was the most insensitive strain isolated in the Wakefield Laboratory until 1970, when two more were recovered in the first 4 months of the year (Little, 1970).

TABLE II *Relationship of sensitivity of strains to relapse rate*
Strains isolated in cases of treatment failure shown in brackets

Year	Fully sensitive	Partially resistant		Relapse rate
		No.	Per cent.	
1964	25	12	32.4	—
1965	39 (1)	9 (1)	23.7	3.9
1966	54 (1)	5	8.4	1.8
Total	118 (2)	26 (1)	18.1	2.1
1966	17 (1)	11 (2)	39.3	11.1
1967	55	30 (2)	35.3	2.6
1968	54 (2)	20 (4)	27.0	9.4
1969	18 (1)	6 (1)	25.0	8.3
Total	144 (4)	67 (9)	31.7	6.8

Table III shows the sensitivity pattern of strains isolated in cases of relapse; there was a preponderance of partially resistant strains in 1966 to 1969.

There was no evidence that PAM fostered the emergence of relatively resistant strains, but this absence of evidence is understandable when such strains were already infrequent in the region of the survey.

TABLE III *Sensitivity of gonococcal strains in cases of relapse*

Strain	Initial isolation	Lost on subculture	Isolation in relapse attack	
			Fully sensitive	Partially resistant
Fully sensitive*	6	3	2	1
Partially resistant†	10	1	—	9
Total	16	4	2	10

*Inhibition by 0.05 units penicillin per ml.

†Growth with 0.05 units but inhibition by 0.5 units penicillin per ml.

Discussion

The correlation between an increase in failure rate and an increase in the proportion of less sensitive strains of gonococci has been noted by many authors

TABLE I *Results of treatment with 0.5 g. probenecid 6-hrly plus 1.2 m.u. PAM or procaine penicillin*

Treatment	Nos. confirmed by culture	No. followed	Relapses	Diagnosed by smears only	Nongonococcal urethritis	Percentage relapse of cases confirmed by culture
1964-1966 PAM plus probenecid	160	143	3	11	25	2.1
1966-1969 Procaine penicillin plus probenecid	216	191	13	39	41	6.8

(WHO, 1969). Warren (1968) drew attention to geographic factors in the distribution of partially resistant strains in the range 0.06 to 0.5 units penicillin per ml., noting 54.5 per cent. of such strains in cases from abroad, 32.4 per cent. in cases from areas of the United Kingdom other than Southampton, and 17.1 per cent. in cases in Southampton. Sensitivity studies by Keys, Halverson, and Clarke (1969) in the Philippines showed that 73 per cent. of 242 strains of gonococci required 0.4 to 1.6 units penicillin per ml. for inhibition. A comparison of some findings from the United Kingdom (Table IV) shows a variable picture, but with a tendency for the proportion of relatively resistant strains to increase in recent years. There is evidence that improving the therapeutic results by raising the dosage of penicillin lowers the prevalence of partially resistant strains (Letchner and Nicol, 1961; Morton, 1963; Ødegaard and Gjessing, 1967); this was particularly well shown by Olsen and Lomholt (1969) in Greenland, who demonstrated a fall in incidence of partially resistant strains from 54 to 19 per cent. after the introduction of treatment with 5 m.u. sodium penicillin G combined with 1 g. probenecid.

There is obviously a continued need for bacteriological monitoring in some (and preferably most) cases of gonorrhoea. Speedy return of results of sensitivity tests alerts the clinician to possible treatment failure in both patient and contacts; comparison of strains assists in distinguishing relapse from re-infection and on occasion there is a marginal bonus for the social worker in her enquiry into the truthfulness of the patients' histories of their sexual contacts.

There remains the paradox of the case in which penicillin at the theoretically appropriate dose fails to eradicate the fully sensitive strain or does eradicate the relatively resistant gonococcus. Willcox (WHO, 1969), in his survey of penicillin failures, included

individual variations in serum levels as a main cause. A close study of twenty patients enabled Krook and Juhlin (1965) to suggest that for effective therapy the concentration in whole blood should preferably be at least ten times the 50 per cent. inhibitory concentration of the gonococcal strain *in vitro*. A full analysis of each case of failure, coupled with further research, may enable us to be more aware of the factors responsible for unduly low or sub-lethal penicillin levels and possible ways of dealing with them.

Summary

(1) In Doncaster, in 1964 to 1966, the treatment of cases of gonorrhoea in men with PAM 1.2 m.u. and probenecid 2 g. in divided doses yielded a relapse rate of only 2.1 per cent.; between 1966 and 1969 (July) treatment with procaine penicillin 1.2 m.u. and probenecid resulted in a relapse rate of 6.8 per cent.

(2) Strains of gonococci partially resistant to penicillin, requiring more than 0.05 unit penicillin per ml. for inhibition, were isolated in 18.1 per cent. of cases during the first period and in 31.7 per cent. during the second.

Though the overall numbers of cases of relapse were small, there was demonstrated a relationship with the presence of partially resistant strains.

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TABLE IV Comparison of prevalence of partially resistant strains

Authors	Date		No. of strains	Inhibition range (units penicillin per ml.)	Percentage of partially resistant strains
	Of publication	Of survey			
Curtis and Wilkinson	1958	1957	302	0.06-0.5	25.1
Cradock-Watson, Shooter, and Nicol	1958	1958	200	0.06-0.5	25.0
	1971	1964-66	118	0.06-0.5	18.1
Present series		1966-69	144	0.06-0.5	31.7
Nicol, Ridley, and Symonds	1968	1966	91	0.08-0.8	47.3
Wilkinson (WHO)	1969	1968	212	0.06-0.5	32.5
Leigh (WHO)	1969	1968	242	0.1-over 0.5	41.3

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P.A.M. et probénécide et pénicilline-procaïne et probénécide dans la gonococcie

SOMMAIRE

(1) Entre 1964 et 1966, à Doncaster, le traitement de la gonococcie masculine avec P.A.M. 1,2 m.u. associée à 2 g. de probénécide en plusieurs doses détermina un taux de rechute de seulement 2,1 pour cent; entre 1966 et 1969 (Juillet) on observa un taux de rechute de 6,8 pour cent avec 1,2 m.u. de pénicilline-procaïne associée au probénécide. (2) Des souches de gonocoques partiellement résistantes à la pénicilline et inhibées seulement par 0,05 u/ml de pénicilline furent isolées dans 18,1 pour cent des cas pendant la première période, et dans 31,7 pour cent pendant la seconde.

Bien que le nombre total des rechutes fut réduit, il apparaît une relation vis-à-vis de la présence de souches partiellement résistantes.